

Impact of omega-3 polyunsaturated fatty acids on cardiovascular system

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Abstract. Long-term prospective cohort studies showed the association between high fish and omega-3 polyunsaturated fatty acids intake and lower risk of cardiovascular disease (CVD), especially coronary heart disease and myocardial infarction, as well as cardiovascular mortality in the general population. This review article analyses some of the key studies that have investigated the use of eicosapentaenoic and docosahexaenoic acids for primary and secondary prevention of CVD, discuss the mechanisms of its potential cardioprotective effects, and evaluates recently published randomized clinical trials in the context of existing scientific literature data.

Keywords: omega-3 polyunsaturated fatty acids, cardiovascular disease prevention, cardiovascular risk.

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Introduction

For the first time, the benefit of omega-3 polyunsaturated fatty acids (PUFAs) has been established in the 70s of the XX century, when the study among the Greenlandic Inuit was published. The Inuit prac-

tically did not have cardiovascular diseases (CVD), atherosclerosis and type 2 diabetes mellitus, unlike Europeans. This phenomenon was associated with their diet that include the consumption of large amount of oily fish rich in omega-3 PUFAs. Subsequently, ep-

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idemiological studies among the indigenous populations of Arctic and among the Japanese confirmed the data obtained among the Greenlandic Inuit. Since then, scientists focused on PUFAs as the factor for CVD prevention and mortality reduction.

The omega-3 PUFAs are the building molecules and are incorporated into cell membranes, and also are involved into such mechanisms as fluidity, permeability, activity of membrane enzymes and receptors and intracellular signal transduction pathways [1]. In addition, PUFAs are involved into metabolic processes and the production of biologically active substances [2, 3].

In this study we aimed to assess the effectiveness of omega-3 PUFAs for primary and secondary CVD prevention. We performed the analysis of scientific literature data according to PubMed and e-library databases. The articles were included only if they were published no more than 10 years ago. The following keywords were used: omega-3 polyunsaturated fatty acids, cardiovascular disease prevention, cardiovascular risk.

Cardioprotective effect of omega-3 polysaturated fatty acids

Cardioprotective effect of omega-3 PUFAs is mainly explained by its the ability to modify CVD risk factors. They are well studied and include: high blood pressure, high triglycerides (TG) levels and low high-density lipoprotein (HDL) cholesterol, endothelial dysfunction, arrhythmias, heart rate, heart rate variability, hypercoagulation and inflammation.

Biological mechanisms for cardioprotective effect of omega-3 PUFAs are associated with alteration of cell membranes properties due to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) incorporation, as well as modulation of protein membrane receptors response. Direct modulation of ion channels by omega-3 PUFAs underlies their anti-arrhythmic effect. They also prevent cytosolic calcium fluctuations in cardiomyocytes by influencing calcium channels of the cytoplasmic reticulum. Omega-3 PUFAs prevent the development of spontaneous depolarization and life-threatening arrhythmias by blocking voltage-gated sodium channels. This effect is mostly pronounced in ischemic cells [4, 5].

EPA and DHA are involved into the synthesis of eicosanoids. Cyclooxygenase contributes to the synthesis of thromboxane A3 and prostaglandin I3 as

well as the reduction of thromboxane A2 and prostaglandin I2 formation from arachidonic acid. The ratio between thromboxane A2 and prostaglandin I2 is of greater importance, since prostaglandin I2 decreases to a greater extent. This shift has antiarrhythmic effect, reduces the risk of ventricular fibrillation and sudden cardiac death. In addition, omega-3 PUFAs reduce the amount of arachidonic acid in the membranes of cardiomyocytes, and, therefore, provide anti-arrhythmic and anti-inflammatory effect [4, 6].

Anti-arrhythmic of omega-3 PUFAs is not only associated with the metabolism of eicosanoids. The incorporation of EPA and DHA into the lipid bilayer of cardiomyocyte's membrane alters its properties and, therefore, affects function of ion channels and enzymes that are incorporated into the cell membrane. The possibility to affect the cellular inositol cycle and modulate calcium release from the endoplasmic reticulum is another mechanism that prevents the development of arrhythmias into the ischemic cell.

In addition, PUFAs affect cellular signal pathways. EPA and DHA can impair the initiation of toll-like receptors [1] that decreases the activation of the transcription of nuclear factor kappa, the level of pro-inflammatory cytokines (tumor necrosis factor, interleukin-18, interleukin-6 and interleukin-8) as well as pro-inflammatory metalloproteinases [3, 6, 7]. In addition, anti-inflammatory effect of omega-3 PUFAs can be explained by the decrease of cell adhesion molecules expression (E-selectin, P-selectin, etc.) that increases stability of atherosclerotic plaques into the arteries. Omega-3 PUFAs can regulate protein expression through peroxisome proliferator-activated receptors (PPARs), α , β , δ , γ , and thereby contribute to anti-inflammatory effect. Activation of PPAR- γ increases insulin sensitivity and enhances glucose metabolism, while activation of PPAR- β , δ enhances fatty acid metabolism. Thus, the peroxisome-activated nuclear receptors play a pivotal regulatory role into lipid metabolism and carbohydrate metabolism [8]. Several studies have described the reduction of blood triglyceride (TG) levels by 20-30% [9, 10] after high daily intake (over 4 g) of EPA and DHA. The pathophysiology of TG reduction is associated with the reduction of its hepatic synthesis and secretion into the blood. In addition, omega-3 PUFAs contribute to the elimination of very low-density lipoproteins by the liver, and the excretion of cholesterol catabolism products along with bile acids [11]. Omega-3 PUFAs

affect the level of total cholesterol, and can reduce it by 8-12%. It is also noteworthy that DHA and EPA have different effects on blood lipids. DHA primarily increases HDL cholesterol level [12]. At the same time, DHA also increases low-density lipoprotein (LDL) cholesterol levels to a greater extent compared with EPA. The researchers noted that this effect is more pronounced in men compared with women [3, 13].

The hypotensive effect of omega-3 PUFAs for both normotonic and hypertensive patients has been mentioned. EPA and DHA reduce arterial stiffness and, therefore, decrease vascular resistance and pulse wave velocity. Activation of NO synthetase causes the increase of the NO production that is the main relaxing factor [14].

Omega-3 PUFAs can influence intracardiac hemodynamics and reduce myocardial remodeling. This effect can be explained by the decrease of diastolic and systolic volumes of the left ventricle, an increase of the ejection fraction and exercise tolerance [15].

The prescription of omega-3 PUFAs reduces platelet aggregation, and, considering the reduction of intracellular adhesion molecules production, can lead to the stabilization of atherosclerotic plaque and provide pleiotropic effect [16].

The effect on myocardial remodeling in patients after acute myocardial infarction has been shown into the OMEGA-REMODEL study, where the use of omega-3 PUFAs was associated with the reduction of negative left ventricular myocardial remodeling, primarily due to the decrease of the end-systolic volume index. The study also established the reduction of the fibrosis degree in the non-infarcted myocardium [17].

Omega-3 index and its interpretation

The consumption of omega-3 PUFAs dietary supplements or food rich in omega-3 is not equivalent to the content of omega-3 PUFAs in the human body, therefore, it is necessary to evaluate the level of EPA and DHA in the human body. The omega-3 index can serve as an objective biomarker for omega-3 PUFAs intake that is the total percentage of EPA and DHA from all measured fatty acids within erythrocyte membranes. This indicator does not depend on diet and correlates with the content of omega-3 PUFAs into the erythrocyte membrane. The omega-3 index ranges from 2% to 20% [18].

Several studies investigated the use of the omega-3 index for cardiovascular risk stratification. The

data obtained indicate that omega-3 index level over 8% is associated with minimal cardiovascular risk, and omega-3 index less than 4% can be interpreted as risk factor for cardiovascular events (fatal and non-fatal myocardial infarction, sudden cardiac death) [19]. It has been shown that high omega-3 index is associated with the decrease of not only cardiovascular mortality, but also all-cause mortality. Thus, in patients with omega-3 index over 6.8%, all-cause mortality was 34% lower compared with those who had omega-3 index less than 4.2%, and the risk of CVD was lower by 39% [18].

Average level of omega-3 index differs between various countries. Regions with high blood levels of EPA+DHA (>8%) include the Sea of Japan, Scandinavia, and areas with indigenous populations not influenced by Westernized dietary habits. Very low blood levels ($\leq 4\%$) have been observed in North, Central and South America, Europe, the Middle East, Southeast Asia and Africa [20, 21].

Omega-3 PUFAs and cardiovascular disease prevention

Over the past 50 years large number of studies assessed the effectiveness of omega-3 PUFAs for primary and secondary CVD prevention. However, the results on the association between omega-3 fatty acid and clinical outcomes for cardiovascular events remain controversial.

For the first time, the possibility to influence recurrent cardiovascular events have been demonstrated in the DART (Diet and reinfarction trial) that showed the reduction in mortality during the 2 years after myocardial infarction among men who were advised to eat about 300 g of oily fish per week, or who took fish oil supplements giving an equivalent amount of n-3 fatty acids. The GISSI Prevenzione study confirmed the results of DART and showed that people who after myocardial infarction took omega-3 PUFAs had 15% lower risk of cardiovascular events, 30% lower relative risk of death from CVD as well as 45% lower risk of sudden cardiac death.

The GISSI-HF study (Studio della Sopravvivenza nell'Insufficienza cardiac — Heart Failure trial) evaluated the impact of PUFAs intake in patients suffering from heart failure. As a result, omega-3 intake was associated with the reduction of all-cause mortality in patients with chronic heart failure by 9% and the

frequency of admissions for ventricular tachyarrhythmia by 28%.

Subsequently, several observational studies examined the relationship between the intake of omega-3 PUFAs and cardiovascular outcomes. However, there is still lack of randomized controlled trials of sufficient duration that have shown cardioprotective effects in healthy people. The open-label JELIS study conducted by the Japan Environmental Protection Agency (Japan EPA) assessed the effect of EPA 1.8 g/day (as ethyl ester) in combination with statins versus statin alone in 18,645 hypercholesterolaemic patients. The primary endpoint was any major coronary event. The study showed that EPA and statin treatment was not superior to statin monotherapy for the primary prevention of major coronary events.

By the end of 2018 another two large randomized controlled trials on primary prevention were published. In the ASCEND (A Study of Cardiovascular Events in Diabetes) 15,480 people with diabetes mellitus without CVD were randomized to receive either marine n-3 fatty acids (840 mg/day EPA + DHA) versus olive oil (placebo) [22]. Two groups did not differ significantly by the incidence of the primary outcome (serious cardiovascular event) during 7-year follow-up.

In the VITAL study, conducted in 25,000 healthy subjects over the 50 (men) and 55 years (women) years old, participants were divided into two groups: group 1 took omega-3 fatty acids (840 mg/day EPA + DHA) and vitamin D (2000 IU/day), group 2 — placebo [23]. The follow-up period was 5 years. As a result, there were no significant differences in the primary outcomes of major cardiovascular events (combined myocardial infarction, stroke, or death from any cardiovascular cause) between the study groups.

The studies OMEGA, Supplementation en Folate et Omega-3 (SU.FOL.OM3), ORIGIN, Risk and Prevention Study evaluated the effectiveness of PUFAs for secondary prevention of recurrent fatal and non-fatal cardiovascular events. All these studies did not show any benefits of omega-3 PUFAs.

Due to conflicting results of studies that evaluated the efficacy of omega-3 PUFAs for primary and secondary prevention of cardiovascular events, large meta-analysis was conducted that included 79 randomized controlled trials (112,059 adult participants with various cardiovascular risks, mainly from high-income countries) lasting from 12 to 72 months. Most

studies compared DHA and EPA supplements with diet rich in omega 3 PUFAs. This meta-analysis found little or no effect of EPA and DHA on all-cause mortality [24]. However, many researchers criticized the meta-analysis, pointing out that several factors were not considered by the researchers and could bias the result. First of all, low doses of omega-3, lack of accounting for the omega-3 index among participants, concomitant lipid-lowering therapy, short follow-up period and a long period between previous cardiovascular event and omega-3 PUFAs administration.

The REDUCE-IT study, published in early 2019, rehabilitated EPA and DHA and included 8,179 participants. The study evaluated the effect of EPA ethyl ester on primary and secondary outcomes. The study participants were divided into 2 groups: the first group took 4 g of EPA (icosapent ethyl) ethyl ester, the second group - placebo with mineral oil. The follow-up period averaged 4.9 years [25]. All patients received statins and had high triglycerides serum level (1.52–5.63 mmol/l). Patients, who received icosapent ethyl, showed statistically significant reduction in the relative risk of cardiovascular events by 25% compared with placebo. Accordingly, participants from icosapent ethyl group had significant reduction of TG and LDL cholesterol compared with placebo after 1-year follow-up. It is also noteworthy that the result in icosapent ethyl group did not depend on the initial TG level or the degree of subsequent TG decrease. This study demonstrated that high dose of EPA (4 g per day) may provide an additional benefit for the reduction of cardiovascular events and mortality.

The interaction between omega-3-polyunsaturated acids

The results obtained in the REDUCE-IT study pose the question on reason for such differences between the effect of various PUFAs on endpoints. There are significant gaps in the knowledge about the interaction between of EPA and DHA, since their effects are primarily assessed together as combination of two PUFAs. Several researchers have evaluated the effects of EPA and DHA on each other. It was found that EPA and DHA may compete for residency in membrane phospholipids, and thereby differentially displace n-6 PUFAs, which are highly prevalent in the population. This influence biophysical membrane properties, affects the synthesis of eicosanoids, activation of cellular signaling pathways and nuclear

receptors. Second, EPA and DHA exert different effects on plasma membrane biophysical structure, creating an additional layer of competition between the fatty acids in controlling signaling. DHA regulates membrane EPA levels. Therefore, there is molecular competition between EPA and DHA, which would ultimately impact outcomes [26]. These data refute the conclusions of some randomized clinical trials and meta-analyses that omega-3 PUFAs (usually administered as combination of EPA and DHA) have no effect on cardiovascular pathology [27, 28].

The REDUCE-IT study confirms the effect of EPA alone. The recent STRENGTH randomized clinical trial evaluated the impact of EPA/DHA mixed carboxylic acids (EPANOVA) in addition to statins on clinical outcomes, the development of any cardiovascular event in particular, in patients with high cardiovascular risk and hypertriglyceridemia. This study was suspended due to lack of evidence of omega-3 PUFAs supplements for cardiovascular benefit [29]. There is a possibility that these results may be due to DHA negating the effects of EPA. Although the administration of EPA alone in the REDUCE-IT study demonstrated good results.

The question on the varying degrees of absorption of different forms of omega-3 PUFAs remains open.

Most dietary supplements are presented in two main forms: re-esterified triglyceride form of omega-3 or omega-3-acid ethyl esters that have varying degrees of absorption and side effects [30, 31]. The esterified monoglyceride form of omega-3 is less prevalent. Although this form has shown advantages since lower dose is needed to increase the concentration of serum PUFAs compared with other forms.

Conclusion

Omega-3 PUFAs have cardioprotective effect based on several well-studied biological mechanisms. Over the past 20 years, a fairly large number of clinical studies have been conducted to investigate the potential of EPA and DHA for the primary and secondary prevention of cardiovascular events in individuals with high and very high cardiovascular risk. The conflicting data reported by different trials can be explained by the use different EPA and DPA forms, low doses, and lack of control for omega-3 index as the key indicator for omega-3 PUFAs absorption. The REDUCE-IT study have shown the effectiveness of EPA ethyl ester in combination with statins for TG levels reduction.

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